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New reactions of oximinocyanoacetamides with benzylamine : A one-pot entry into isoxazole nucleus

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4-Amino-5-benzoylisoxazole-3-carboxamide and its 3-(*N*-methyl) analogue **7** have been prepared in one-pot from oximinates, which, in turn, are prepared in a hitherto unreported way from oximinocyanoacetamides (**2**) and benzylamine.

In connection with our studies on nitrogen heterocycles using oximinocyanoacetamides[1] we required 2-phenyl-5-aminoimidazole-4-carboxamide **1** for quanternisation and subsequent hydrazine-mediated ring expansion for a convenient entry into 1,2,4-triazine nucleus of the antibiotics, toxoflavin and fervenulin[2]. We envisaged that annulation[3] of benzylamine with oximinocyanoacetamides **2a-c** might lead to **1**. To our surprise, however, stable oximinates and amidines were obtained instead of the expected imidazoles. The present investigation deals with the characterisation of the products and utilisation of the oximinates for a convenient and one-pot synthesis of the substituted isoxazole **7**.

The treatment of **2a** in CH_3CN with benzylamine at rt led to the crystalline salt **3a**, identified from spectral data. The *N*-methyl substrate, **2b** furnished in a similar fashion the corresponding *N*-methyl salt, **3b**. The regeneration of **2a** and **2b** from the corresponding salts by treatment with HCl supported the structures assigned to the former. The fusion of the oximinates or the fusion or refluxing in CH_3CN of **2a** and **2b** with benzylamine furnished the respective amidines **4a** and **4b**, probably through a tandem disproportionation - recombination sequence (Scheme I). The corresponding ethyl ester **2c** failed to react with benzylamine under any of the aforesaid conditions.

In a meaningful utilisation of the amidine **4a**, it was attempted to be cyclised to the pyrimidine derivative by treatment with ethyl orthoformate in refluxing CH_3CN, but to no avail. Ethyl chloroformate, however, afforded the only product **5** with **4a** in hot pyridine, but attempts to cyclise **5** met with failure. Existence of **5** in the oximino form, as evinced by spectral analyses, probably prevents further cyclisation. The compound **4b**, however, failed to react with ethyl chloroformate in identical condition.

The aforesaid failure prompted us to try to exploit the oximinate **3a** for cyclisation through its *O*-phenacyl derivative. Accordingly, **3a** was first converted ($PhCOCH_2Br/CH_3CN$) to the phenacyloxy derivative **6a** in nearly quantitative yield. It was then easily cyclised to the isoxazole, **7a** by treatment with tetrabutylammonium iodide (TBAI), in dil. alkali (Scheme II). It is interesting to note that **2a** did not afford **6a** directly with phenacyl bromide.

To test the generality of this reaction, **6b**, obtained from **3b** essentially as described, was treated similarly with dilute alkali in presence of TBAI when **7b** was obtained in moderate yield.

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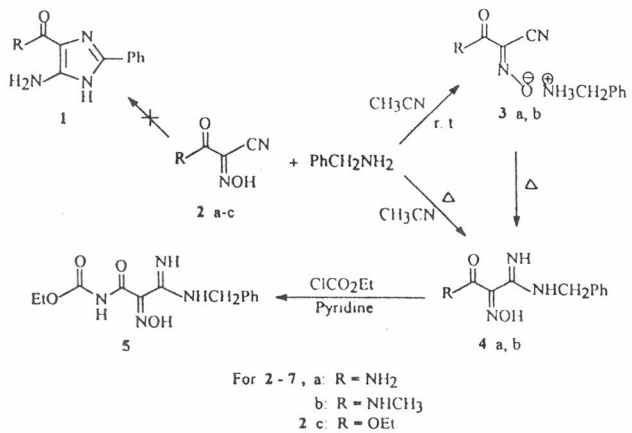
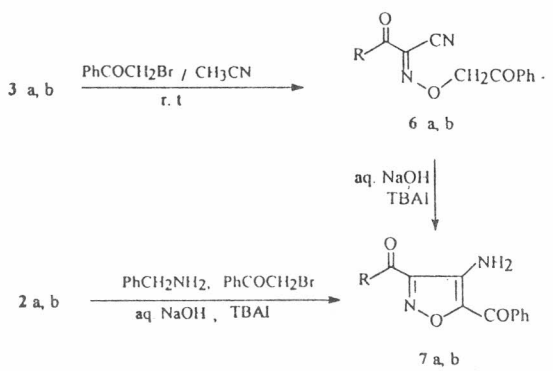


Scheme I



Scheme II

For both **7a** and **7b**, the yields were better when they were prepared directly from **2a** and **2b**. The earlier method[4] for the synthesis of isoxazole carboxamide starting from the sodio salt, **2a** in DMF, was an elaborate process. Our method, which involves *in situ* utilisation of the intermediates, is straight forward and considerably better than the reported one. The present communication thus constitutes a convenient synthesis of 4-amino-5-benzoylisoxazole-3-carboxamides directly from oximinocyanoacetamides.

The extensive use[5,6] of isoxazoles as pharmaceuticals and in agriculture as well as their application as intermediates in the the synthesis of pharmacologically useful fused heterocycles assumes importance for our observation recorded herein.

Experimental Section

IR spectra were recorded as KBr pellets on a Perkin-Elmer 599-B Spectrophotometer. Mass spectra refer to EIMS, recorded in a AEI MS-30 double-beam spectrometer. ^{1}H and ^{13}C NMR spectra (multiplicities determined by BBD and DEPT 135 spectra) were recorded in $(CD_3)_2SO$ solution using Me_4Si as internal standard on Bruker AM300 spectrometer unless otherwise stated.

Synthesis of the oximinate 3a. Benzylamine (0.53 g, 5 mmole) was added all at once to a well stirred solution of **2a** (0.56 g, 5 mmole) in dry CH_3CN (5 mL), when the reaction became exothermic, and a crystalline solid started separating from the yellow solution. It was filtered, washed thoroughly with diethyl ether and dried on a steam bath to afford **3a** (0.8 g), m.p. 129-30°; IR (KBr): 3400, 3320, 3200, 2200, 1670 cm^{-1}; ^{1}H NMR: δ 7.33-7.47 (5H, m, Ar-*H*), 7.27 (1H, br, exch.), 4.0 (2H, s, N-C*H*$_2$Ph); ^{13}C NMR: δ 165.70 (s), 135.38 (s), 128.55 (x3), 128.16 (x2), (all d, Ar-CH), 127.42 (s), 113.78 (s), 42.75 (t).

Synthesis of the oximinate 3b. It was prepared on the same scale and in a similar manner as in the case of **3a**. The product **3b** appeared as yellow solid (0.9 g), m.p. 119-20°; IR (KBr): 3330, 2220, 1620 cm^{-1}; ^{1}H NMR: δ 7.37 (5H, s, Ar-*H*), 6.75 (1H, br, exch.), 4.0 (2H, s, N-C*H*$_2$Ph), 2.70 (3H, d, *J*=6 Hz, NH C*H*$_3$).

Synthesis of the amidine 4a: Method A. A mixture of **2a** (0.8 g, 7.1 mmole) and benzylamine (0.8 g, 7.4 mmole) in CH_3CN (8 mL) was heated under reflux for 5 hr. The solvent was then removed under reduced pressure and the residue was triturated thoroughly with water. The resulting solid was filtered and crystallised from ethanol to afford **4a** (1.1 g, 76%) as yellow shining crystals, m.p. 211-12° (Found: C, 54.3; H, 5.6; N, 25.2. $C_{10}H_{12}N_4O_2$ requires C, 54.5; H, 5.4; N, 25.4%); IR (KBr): 3425, 3270, 3180, 1655, 1600 cm^{-1}; ^{1}H NMR: δ 10.93 (1H, br, exch.), 7.56 (1H, br, exch.), 7.31-7.20 (5H, m, Ar-H), 6.87 (1H, br, N*H*CH$_2$Ph, exch.), 4.53 (2H, d, *J*=12 Hz, NHC*H*$_2$Ph); ^{13}C NMR: δ 170.4, 152.9, 136.2 and 135.6 (all s), 128.7 (x2), 127.6, 127.4 (x2) (all d, Ar-C*H*), 43.1 (t); MS (m/z): 220 (M$^+$), 203, 186, 176, 160, 159, 158, 106, 91.

Method B. A mixture of **2a** (0.56 g, 5 mmole) and benzylamine (0.58 g, 5.4 mmole) was heated in an oil bath at 130-35° for 1 hr. The mixture was

then cooled to rt and the resulting sticky mass was triturated with warm aq. ethanol and worked up as usual to afford **4a** (0.9 g, 60%).

Method C. 4a was obtained in 50% yield from the direct fusion of the oximinate **3a** essentially as described above in Method B.

Synthesis of amidine 4b: Method A. A mixture of **2b** (0.63 g, 5 mmole) and benzylamine (0.58 g, 5.4 mmole) in CH_3CN (6 mL) was heated under reflux for 3 hr and worked up as usual to furnish **4b** in 75% yield (0.8 g), m.p. 179-80° (MeOH) (Found: C, 56.6; H, 6.0; N, 24.2. $C_{11}H_{14}N_4O_2$ requires C, 56.4; H, 5.9; N, 23.9%); IR (KBr): 3420, 3240, 1650, 1600 cm^{-1}; ^1H NMR: δ 10.79 (1H, br, exch.)_, 7.56 (1H, br, exch.), 7.35-7.20 (5H, m, Ar-*H*), 6.34 (1H, br, N*H*CH_2Ph, exch.), 4.50 (2H, d, *J*=12 Hz, NHC*H*$_2$Ph), 2.82 (3H, d, *J*=6 Hz, NHC*H*$_3$); ^{13}C NMR: δ 168.10, 154.0, 135.4, 134.4 (all s), 129.2 (x2), 128.3 (x1), 127.2 (x2) (all CH), 44.2 (t), 25.5 (q); MS (m/z): 234 (M^+), 217, 186, 176, 160, 159, 158, 106, 91.

Methods B and C. Following essentially the same procedures as described earlier in the case of **4a**, the product **4b** was obtained in 60% and 58% yields, respectively.

Reaction of 4a with ethyl chloroformate. A mixture of **4a** (0.5 g, 2.3 mmole) and ethyl chloroformate (0.3 g, 2.7 mmole) in pyridine (2 mL) was stirred at 60° for 1 hr. The resulting clear solution was then cooled to rt, diluted with water and the resulting crystals were filtered. The product was purified by recrystallisation from ethanol to afford **5** in 80% yield (0.5 g), m.p. 180-82° (Found: C, 53.12; H, 5.07; N, 18.91. $C_{13}H_{16}N_4O_4$ requires C, 53.42; H, 5.47; N, 19.17); IR (KBr): 3420, 3400, 3200, 1750, 1700, 1600 cm^{-1}; ^1H NMR: δ 13.3 (1H, br, CON*H*CO, exch.), 7.40-7.20 (5H, m, Ar-*H*), 6.80 (1H, br, N*H*CH_2Ph, exch.), 4.52 (2H, d, *J*=12 Hz, NHC*H*$_2$Ph), 4.28 (2H, q, *J*=6 Hz, OC*H*$_2$CH$_3$), 1.18 (3H, t, *J*=6 Hz, OCH$_2$C*H*$_3$).

α-Cyano-α-phenacyloxyiminoacetamide 6a. **3a** (1.1 g, 5 mmole) was dissolved in CH_3CN (10 mL) by slight warming, cooled to rt and to this was added a solution of phenacyl bromide (1 g, 5 mmole) in CH_3CN (2 mL) all at once. The reaction became exothermic and almost immediately a white solid separated. It was filtered, washed with cold ethanol, dried and recrystallised from ethyl acetate to afford white shining crystals of **6a** (1.1 g, 98%), m.p. 204-205°[4]; IR (KBr): 3360, 3160, 2920, 2250 (W), 1710, 1690 cm^{-1}.

α-Cyano-α-phenacyloxyimino-*N*-methylacetamide 6b. 6b was obtained from **3b** and phenacyl bromide essentially as described above, and yield was nearly quantitative, m.p. 160-62° (EtOH) (Found: C, 58.27; H, 4.28; N, 17.04. $C_{12}H_{11}N_3O_3$ requires C, 58.77; H, 4.48; N, 17.14%); IR (KBr): 3340, 3060, 2980, 2940, 2240, 1700, 1690 cm-1; ^1H NMR (100 MHz): δ 8.24 (1H, br, exch.), 7.32-7.72 (5H, m, Ar-*H*), 4.0 (2H, s, C*H*$_2$CO), 2.67 (3H, d, *J*=6 Hz, NHC*H*$_3$).

4-Amino-5-benzoylisoxazole-3-carboxamide 7a: Method A. A mixture of **6a** (0.23 g, 1 mmole), tetrabutylammonium iodide (50 mg) and 2% NaOH (3 mL) was stirred at rt for 3 hr. The solid obtained was collected by filtration, washed well with water and dried. It was then dissolved in hot ethanol, stirred with charcoal for 15 min and filtered hot. The filtrate was concentrated and cooled to obtain shining crystals of **7a** (0.1 g, 43%); m.p. 200-201°[4].

Method B. (One-pot preparation directly from **2a** via *in situ* generation of **3a** and **6a**). Benzylamine (0.5 g, 5 mmole) was added to a mixture of **2a** (0.5 g, 4.4 mmole) in dry acetonitrile (5 mL) taken in a centifuge tube, when immediately a crystalline solid separated out. It was then cooled to rt, centifuged and the supernatant decanted off. The residue was leached thoroughly with ether to remove adhering benzylamine, centrifuged again to obtain a solid (**3a**) which was then dissolved in warm acetonitrile (8 mL) and treated with phenacyl bromide (1 g, 5 mmole) all at once. A white precipitate was instantaneously obtained, cooled to rt, centrifuged and the supernatant liquid removed. The precipitate was thoroughly leached with acetonitrile and the last traces of the solvent was removed under suction. The residue (**6a**) was then treated with tetrabutylammonium iodide (100 mg) and 2% NaOH solution (6 mL), worked up essentially as described above under Method A to afford **7a** in 50% yield (mixed m.p. unchanged with the sample obtained in Method A) (Found: C, 57.56; H, 4.11; N, 18.34. $C_{11}H_9N_3O_3$ requires C, 57.14; H, 3.89; N, 18.18%); IR (KBr): 3480, 3400, 3380, 3180, 1710, 1650 cm^{-1}; ^1H NMR: δ 8.2-8.44 (2H, br, exch.), 7.6-8.16 (5H, m, Ar-*H*), 6.36 (2H, s, N*H*$_2$, exch.).

4-Amino-5-benzoylisoxazole-3-(*N*-methyl)carboxamide 7b. 7b was prepared identically by Method A and Method B as described above under **7a**, in 45% and 50% yield, respectively; m.p. 141-42° (EtOH) (Found: C, 58.97; H, 4.50; N, 17.34. $C_{12}H_{11}N_3O_3$ requires C, 58.77; H, 4.48; N, 17.14%); IR (KBr): 3480, 3380, 1695, 1650 cm^{-1}; ^1H NMR: δ 8.84-9.0 (1H, br, exch.), 7.60-8.04 (5H, m, Ar-*H*), 6.36 (2H, s, NH_2, exch.), 2.82 (3H, d, *J*=6 Hz, $NHCH_3$).

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References

1 Chattopadhyay G & Saha T K, *J Chem Res (S)*, **1995**, 76.
2 Temple C (Jr) & Montgomery J A, *J Org Chem*, 34, **1969**, 2102.
3 Veronese A C, Cavicchioni G, Servadio G & Vecchiati G, *J Heterocycl Chem*, 17, **1980**, 1723.
4 Gewald K, Bellmann P & Jansch H J, *Liebig's Ann Chem*, **1980**, 1623.
5 Lang S A (Jr) & Lin Y-i, in *Comprehensive heterocyclic chemistry*, Vol. 6, edited by A R Katritzky & C W Rees (Pergamon Press, Oxford), **1984**, p. 127.
6 Short K M & Ziegler C B, *Tetrahedron Lett*, 34, **1993**, 75 and references cited therein.